

## **Psychiatric Drugs Bind to Classical Targets within Early Exocytotic Pathways: Therapeutic Effects**

### ***Supplementary Information***

#### **An mGluR2 Agonist**

Recent studies show that heterodimers between 5-HT<sub>2A</sub> and a metabotropic glutamate receptor (mGluR), mGluR<sub>2</sub>, occur in cortical neurons, that they display unique functional interactions between the individual monomers, and that the contacts occur via transmembrane helices 4 and 5 of mGluR<sub>2</sub> (1, 2). The diacidic mGluR<sub>2/3</sub> agonist LY404039 shows promise in animal models for psychiatric disorders when given acutely (< 6 h before the test). A prodrug of this molecule has yielded partially promising clinical trials for schizophrenia over a 4-wk period (3, 4). It is not known whether LY404039 enters neurons or the endoplasmic reticulum (ER) via dicarboxylate carriers. If so, LY404039 would interact in the ER with mGluR<sub>2</sub> or mGluR<sub>2</sub>-5HT<sub>2A</sub> receptors during the several weeks leading to clinically effective therapy; and although its pharmacokinetics differ markedly from those of the typical and atypical antipsychotic drugs, it would bind to its target in the early exocytotic pathway.

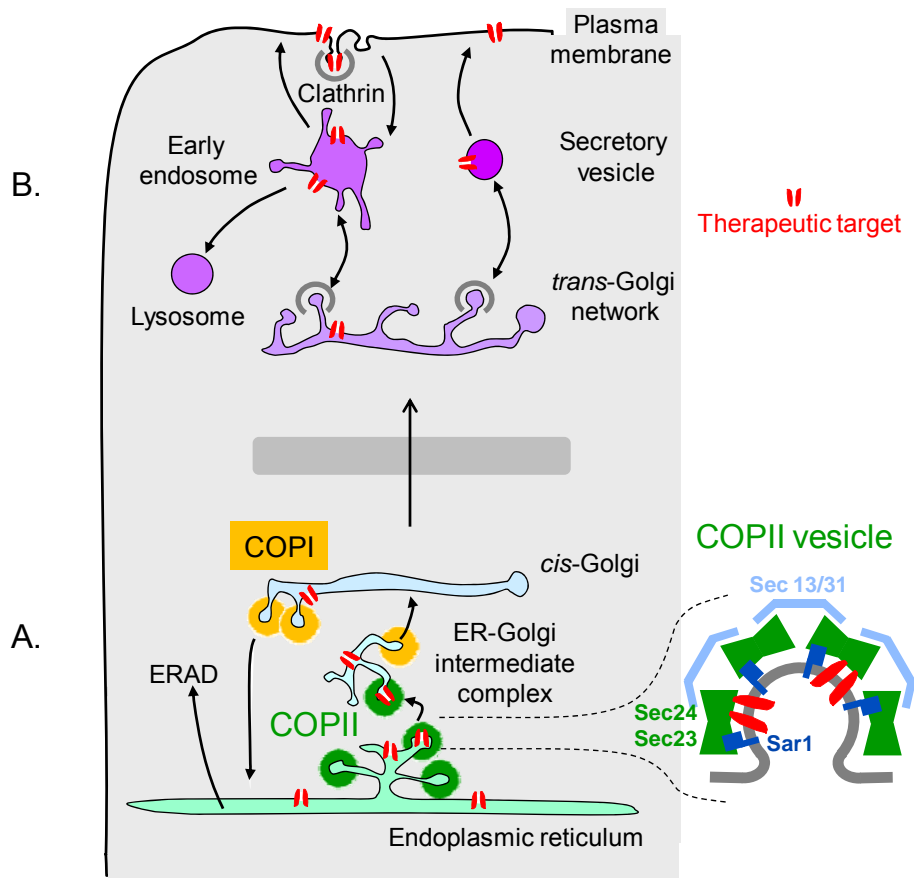
#### **Does Ketamine Block *N*-methyl-D-aspartate (NMDA) Receptors at the Concentrations Used for Depression?**

All investigators agree that ketamine exerts its "rapid" antidepressant effects at "sub-anesthetic" concentrations; yet are these sufficient to block plasma membrane NMDA receptors? We comment on the concentrations of NMDA blockers required to exert the "rapid" antidepressant effect. A clinical trial showed effective antidepressant

activity for a bolus of 0.5 mg/kg (5); in mouse, the effective dose was 3 mg/kg (6). Pharmacokinetic measurements show that the half-life of ketamine in human and mouse brain is 186 and 13 min, respectively (7, 8), and suggest that, averaged over the first 30 min of action, the expected brain concentrations of ketamine are 100 and 300 ng/ml respectively, corresponding to 0.4 to 1.2  $\mu$ M. This would block less than half of NMDA receptors (9, 10). We conclude tentatively that data are more consistent with the presence of another, tighter binding mode for the ketamine-NMDA receptor interaction; and throughout this essay we have argued that this additional mode could well occur in the ER. We note, however, that the details of “trapping block” at ligand-gated channels are modified by the binding and dissociation kinetics, by the fractional activation of the channel, by polyamine and glycine concentrations, and by the transmembrane voltage, leading to the possibility that ketamine does indeed block NMDA receptors completely at the clinically useful doses.

**Table S1.** Pharmacological chaperoning of G protein-coupled receptors by cell-permeant ligands.

Receptor	Mutant / Wild-type	Drug	Reference
adenosine A1	mutant	agonists; antagonists	(11)
dopamine D4	both	transported dopamine; quinpirole; antagonists	(12)
gonadotropin-releasing hormone	mutant	antagonists	(13)
histamine H2	both	agonist, inverse agonist	(14)
opsin	mutant	--	(15)
$\delta$ -opioid	mutant	antagonist	(16)
$\mu$ -opioid	mutant	agonists, antagonists	(17)
melanin concentrating hormone	mutant	antagonist	(18)
melanocortin-4	both	antagonist, inverse agonist	(19)
vasopressin V1a	both	antagonist	(20)
vasopressin V1b/V3	both	antagonist	(21)
vasopressin V2	both	antagonists	(22)



**Figure S1.** Most ideas about psychiatric therapeutics concentrate on (B), the late exocytotic / endocytotic pathway (henceforth called simply “late exocytotic pathway”). This review emphasizes (A), the early exocytotic / retrieval pathway (these are henceforth called simply the “late” “early exocytotic” pathways). G protein-coupled receptors (GPCRs), transporters, and ligand-gated channels are synthesized within the ER and glycosylated within the Golgi apparatus. Therapeutic targets, and the membranes that contain them, undergo budding, transport, reverse transport, and fusion trafficking in (A), in some ways analogous to the well-studied later steps in (B). SNARE proteins and vesicle budding participate in both pathways. In pathway (A), proteins leave the ER via either endoplasmic reticulum-associated degradation (ERAD) or via coated protein II complex (COPII) vesicles (23) (one shown enlarged at right, with its five major proteins (24)). The cargo (in this case a therapeutic target) binds directly to Sec24. COPII vesicles move from the ER to the ER-Golgi intermediate complex. COPI vesicles move from the Golgi to the ER. The components of ERAD, including the ubiquitin ligases, retrotranslocons, and proteasomes, are not shown. This review does not concern classical signal transduction by the receptors, which is thought to occur primarily at the plasma membrane via GPCRs and ligand-gated channels (but see (25)). Via the unfolded protein response, pathway (A) communicates directly with gene activation and protein synthesis (See figures in the main paper).

## Supplemental References

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